REMARKS

The present response is intended to be fully responsive to all points of objection and/or rejection raised by the Examiner and is believed to place the application in condition for allowance. Favorable reconsideration and allowance of the application is respectfully requested.

Status of Claims

Claims 24-28 are currently pending, in the application, with claim 24 being the independent claim. Claims 1-23 and 29 were previously canceled. No claims are amended.

CLAIM REJECTIONS

35 U.S.C. § 112 Rejections

The Office Action, at pages 2-16, maintains the rejection of claims 24-28 under 35 U.S.C. § 112, first paragraph, as allegedly failing to comply with the enablement requirement. Specifically, the Examiner alleges that induction of organized, functional bone formation at a site of bone infirmity by implanting BMP-2-expressing mesenchymal stem cells (MSCs) in the absence of a support osteoinductive matrix is not enabled by the art or the instant specification. Applicants respectfully traverse this ground of rejection.

The Enablement Requirement

To be enabling, the specification of a patent must teach those skilled in the relevant art how to make and use the full scope of the claimed invention without undue experimentation. Enzo Biochem, Inc. v. Calgene Inc., 188 F.3d 1362, 1371 (Fed. Cir. 1999). The specification must provide sufficient detail to enable others to understand and carry out the invention. However, those of skill in the art may use their knowledge of the prior art and routine experimentation to "fill gaps, interpolate between embodiments, and perhaps even extrapolate beyond the disclosed embodiments, depending on the predictability of the art." *Chiron Corp. v. Genentech*, 363 F.3d 1247, 1253 (Fed Cir. 2004). Experimentation is permitted so long as it is not undue. *In re Wands*, 858 F.2d 731,737 (Fed. Cir. 1988). Furthermore, the law does not require working examples. *In re Borkowski*, 422 F.2d 904, 908, 164 USPQ 642, 645 (CCPA 1970).

The Specification Provides Full Enablement for the Claimed Invention

Examples 1 and 2 in the specification clearly show successful bone differentiation following transplantation of pluripotent stem cells transfected with BMP-2 in the absence of an exogenous

osteoinnductive matrix. In particular, Example 1 teaches that transplantation of pluripotent cells transformed with BMP-2 into the abdominal muscle leads to *in vivo* formation of bone collar and cartilage, prominent trabecular bone, cartilage and bone marrow, without the addition of an osteoinductive matrix. Further, Example 2 in the specification teaches that transplantation of pluripotent cells transfected with rhBMP-2 into a segmental defect results in the formation of ectopic bone in the absence of an exogenous osteoinductive matrix.

The lack of requirement for an osteoinductive matrix demonstrates that the transfected cells of the present invention possess an intrinsic ability to generate new bone tissue, a new and unexpected property. Accordingly, the specification provides full enablement for bone formation following implantation of transfected cells without a matrix.

Furthermore, contrary to the Examiner's allegation that Applicants' own work, Moutsatsos, provides evidence that only co-implantation with an osteoinductive matrix leads to the induction of functional bone formation (Office Action at page 5), Moutsatos discloses the following:

> Expression of rhBMP-2 in C3H10T1/2 cells can induce differentiation of osteoblastic and chondroblastic cells. These genetically engineered mesenchymal stem cells have an enhanced therapeutic effect in healing bone segmental defect due too a dual mechanism: the paracrine mechanism of rhBMP-2 on host cells and the autocrine mechanism of rhBMP-2 inducing the osteogenic differentiation of the transplanted genetically engineered stem cells themselves.

Id. Paragraph bridging pages 449-50.

In addition, Moutsatsos teaches:

> Formation of bone by transplanted C9 cells expressing rhBMP-2 was achieved regardless of the carrier being used. C9 cells formed bone when transplanted on a biodegradable collagen carrier and ***even with no carrier at all when injected locally***.

Id, at page 460, col. 1 (emphasis added).

Accordingly, Applicants' own work clearly demonstrates the ability of mesenchymal stem cells transfected with BMP-2 to induce bone formation in the absence of any matrix.

Moreover, as previously stated, Examples 3, 8, 9, 11 and 14-15 clearly show that implantation of collagen sponge alone or collagen sponge loaded with cells not expressing BMP-2 causes no bone formation. Contrary to the Examiner's allegation, nowhere do these examples show that the collagen sponge carrier used in the invention becomes osteoinductive.

The Office has not met the Burden of Showing the Need for Undue Experimentation

First and foremost, Applicants assert that the burden is on the Office to provide a clear reason as to why undue experimentation would be required for the skilled artisan to make and use the claimed invention. *See In re Angstadt*, 537 F.2d 498, 504 (C.C.P.A., 1976). In light of the following, Applicants submit that the Office has failed to meet this burden.

The Office cites the following references as evidence.

- Wolfe *et al., Med Prog Technol 20*:155-68 (1994) ("Wolfe")
- Bruder *et al., J Cell Biochem 56*:283-294 (1994) ("Bruder")
- Leach *et al., Expert Opin Biol Theor 4*:1015-27 (2004) ("Leach")
- Moutsatsos *et al., Mol Ther 3*:449-461 (2001) ("Moutsatsos")

The Office contends that the claims "practically recite implanting MSCs in the absence of any matrix," and that implanting MSCs without a matrix is not enabled by the art or the instant specification. Further, the Office states that even if a carrier is not "osteoinductive" (as defined in Wolfe) prior to implantation at the site of bone infirmity, the mere addition of BMP-expressing MSCs to the matrix will render it "osteoinductive."

The Office's logic, however, is flawed, because the claims encompass the practice of a number of steps, not what occurs in the body after the final step is performed. Specifically, the claims recite the step of "implanting said cultured mesenchymal stem cell in the absence of an exogenously supplied osteoinductive matrix at a site of bone infirmity." Therefore, at the time the cells are implanted, the matrix *that the Office contends will hypothetically becomes osteoinductive* is still **not** osteoinductive. Accordingly, the claims cover the use of nonosteoinductive matrices along with no matrix at all.

The Office Failed to Provide Support for the Allegation that
Non-Osteoconductive Matrices Become Osteoconductive

The Office allges that "[o]nce in contact with MSCs genetically engineered to express and secrete BMP-2, non-osteoinductive matrices necessarily become osteoinductive." But the Office has provided no evidence that this will actually occur. In fact, it is possible that the matrix remains inert while the cells are the sole osteoinductive factor. Either way, the fact that the expression of BMPs by the claimed cells may eventually render a nonosteoinductive matrix osteoinductive is immaterial to the pending claims. The claims recite a method that may include the implantation of a matrix along with the cells, so long as that matrix is not osteoinductive when it is implanted.

The Cited References do not Support the Lack of Enablement Allegation

The Office contends that Wolfe states that "bone formation cannot occur by simply implanting BMP-expressing MSCs in the absence of a support matrix." This is incorrect. Wolfe does not even

discuss the therapeutic delivery of cells, let alone BMP-expressing MSCs. Wolfe's discussion of BMP induction of bone growth is limited to the delivery of osteogenic proteins themselves. Therefore, Wolfe's statement regarding the necessity of using a carrier substance is not relevant to the instant claims, which recite cells. One of skill in the art would clearly understand that the solubility of a protein therapeutic (Wolfe's reason for the necessity of a carrier) would not apply to the delivery of BMP-expressing cells. In fact, the cells perform at least some of the purposes of Wolfe's proposed carrier. The MSC cells of the instant invention release BMP-2 over time and protect BMP-2 from non-specific proteolysis, just as with Wolfe's carrier.

The Office contends that Bruder teaches that organized functional bone formation cannot place by simply implanting cells without a matrix, quoting the following passage "in order to effect osseous repair in a local defect, the cells must be delivered to the site in an appropriate carrier . . . We envision the ideal vehicle as . . . osteoconductive to foster integration . . .." First, Applicants note that Bruder is not discussing BMP-expressing MSCs in this passage. Second, Bruder clearly states that the matrix need not be osteoinductive, but can instead be osteoconductive. Therefore, Bruder does not teach that an osteoinductive carrier must be used in order to obtain organized functional bone formation. And even arguendo that Bruder did explicitly state that, in their hands, they needed a carrier, its teachings are clearly contradicted by the instant specification, which shows bone growth and MSC retention in the absence of any carrier at all.

Finally, the Office cites Leach, stating that there is a problem with transplanting bone-forming cells because of their potential to migrate away from the repair site. Applicants do not dispute that carriers are an effective means for retaining cells at a repair site. But the fact that carriers work well does not mean that the MSCs of the instant invention cannot induce bone repair in their absence.

The Specification Provides Enabling Examples

The Office complains that Applicants have only provided two working examples of their claimed invention—but those are two more than is necessary. *See In re Borkowski*, 422 F.2d. at 737. All Applicants must provide is a teaching that provides a person of skill in the art with a reasonable expectation of success of practicing the claimed invention without undue experimentation. As stated above, this burden has been met. In particular, the showing that the cells are localized to a bone defect gap site one week after transplantation is clear evidence that the cells are being retained—a key requirement for the carriers recited in Bruder, Wolfe, and Leach.

Finally, the Office mischaracterizes Applicants' own work by stating that Moutsatsos provides evidence that only co-implantation with an osteoinductive matrix leads to the induction of functional bone formation. As pointed out in Applicants' previous reply and above, Moutsatsos clearly states that "C9 cells formed bone when transplanted on a biodegradable collagen carrier and even with no

carrier at all when injected locally." This is supported by the data provided in Figure 6(g), which shows that "transplanted C9 cells were found lining newly formed bone trabeculi in the defect sites displaying the morphology of osteoblasts and expressing both β-gal and BMP-2 . . ."

Taken singly or together, the references cited by the Office simply state that carriers are a good way to deliver osteogenic proteins or cells. Again, Applicants don't dispute this fact. But not a single one of these references shows any evidence that the methods of the invention won't work as claimed. They do not show the failure of any claimed methods, nor do they provide any reason why a person of ordinary skill in the art could not achieve organized functional bone formation by following the steps laid out in the claims. At best, they suggest that the use of a carrier may be more effective than no carrier, and at worst, they are entirely not relevant.

The instant application teaches everything one of skill in the art would need to know to practice the invention. It clearly provides evidence that the transformed MSCs of the claims can induce organized bone formation in muscle tissue (Example 1), and that these same cells are retained at the site of bone segmental defects after one week (Example 2). This information shows that the major goals of using carriers (cell and protein retention) are achieved with the BMP-expressing MSCs alone. Given this teaching, the specification provides clear evidence that BMP-2 can induce organized bone formation, and that the same MSCs that induce organized bone in muscle also induce organized bone in bone defects, such as the one described in Example 2. Applicants need not disclose more to provide those of skill in the art with the requisite expectation of success in practicing the claimed invention. The Office's requirement that the claimed invention be exemplified in multiple embodiments is not the legal standard for enablement and is impermissible.

Thus, at least for all the reasons stated above, the rejection of claims 24-28 under 35 USC § 112, first paragraph, is improper. Reconsideration and withdrawal of this ground of rejection are therefore respectfully requested.

Conclusion

All of the stated grounds of rejection have been properly traversed or rendered moot. Thus, the present application is in condition for allowance. Favorable reconsideration and allowance of the claims is therefore respectfully requested.

Should the Examiner have any question or comment as to the form, content or entry of this Amendment, the Examiner is requested to contact the undersigned at the telephone number below. Similarly, if there are any further issues yet to be resolved to advance the prosecution of this application to issue, the Examiner is requested to telephone the undersigned counsel.

Please charge any fees associated with this paper to deposit account No. 50-3355.

Respectfully submitted,

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